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A Consideration of Poliomyelitis, Transfer Experiments, and the Inclusion Bodies Produced By Toxic Substances

RALPH R. SCOBEY, M.D.
Syracuse, N. Y.

The term "virus infection" has been applied without justification to a number of human, animal, and plant diseases. Not only has the virus etiology of certain diseases been assumed in case a substance from one species of animal or plant can be transferred to the same or another species, producing thus an abnormal reaction but the explanation is also loosely applied, in the absence of a demonstrable transferable agent, to disease in which a bacterial etiology cannot be shown. The continued insistence that a virus is responsible for certain diseases appears to have retarded investigation along broad lines and thus research to determine the true etiological factor or factors responsible for these diseases has been seriously handicapped.

This insistence on the virus etiology of certain diseases, based upon the demonstration that a substance obtained from human sources will produce a disease in animals, is best illustrated by the exclusive research on the cause of poliomyelitis. The writer[1–6] has pointed out in contrast to the generally considered virus etiology, that this disease doubtless results from the presence of a toxin in food and water during epidemics and that the so-called virus is the result of the poisoning, and not the primary cause of the disease. The virus theory of poliomyelitis, which has been merely a working hypothesis for the past forty years, has failed to explain its pathogenesis. This fact appears to indicate that some factor, other than a virus, is responsible for the disease.

It is the purpose of this report to show that this factor is beyond doubt a poison. Evidence will be presented to show that "viruses" can be produced in the body by poisons; and that inclusion bodies, which supposedly indicate products of virus activity or the elementary virus bodies themselves, can be found in poisoned animals.

TRANSFER EXPERIMENTS IN PLANTS AND ANIMALS

A transfer experiment on plants that demonstrates the ability to produce an abnormal reaction in a heterologous species with normal material was carried out by Johnson.[7] Although such an experiment might be of didactic interest, it is questionable whether or not it has any practical application.

Johnson (1935) showed that almost all strains of potato under cultivation in America "carry" a virus, for extracts of American potato plants inoculated into tobacco and certain other solanaceous plants will regularly

produce a disease having the properties of a virus infection. Such virus commonly produces no symptoms in potatoes; but after several passages through tobacco its virulence may be exalted until it can cause disease when inoculated back to its original host.

An outstanding example of the development of disease in experimental animals by transfer experiments has been shown in the investigation of the paralytic accidents that occasionally result from rabies prophylaxis and treatment. The writer[6] has considered these investigations in detail elsewhere.

Briefly stated, paralysis has occasionally resulted in animals and humans from the injection of rabies vaccine. These paralytic accidents are in no way related to the date of severity of the original injury but are definitely associated in time with the commencement of the treatment; about all occur 7 to 23 days of the first inoculation. Fatal cases show no rabic virus in the nervous structures.

Investigations by a number of workers during the past fifty years have shown that the injected nervous tissues themselves rather than a virus are responsible for these paralytic accidents. The pathological picture of the nervous system after the injection of normal homologous and heterologous nervous tissues, in these investigations, not infrequently resembled that observed in poliomyelitis. Further, a febrile reaction and an increased cell count in the spinal fluid has been observed. Normal homologous and heterologous nervous structures, not a virus, was shown to be the etiological factor in the production of these paralytic accidents. It has been possible also, as will be shown later, to produce inclusion bodies by the injection of normal brain material. These observations would appear to indicate that unwarranted conclusions probably resulted from investigations by Landsteiner[8] (1908) who showed that an emulsion of spinal cord material from a victim of poliomyelitis could produce, when injected into animals, a disease which resembles human poliomyelitis. This work of Landsteiner still stands as the basis of the virus theory of poliomyelitis.

The so-called kidney virus and the submaxillary gland virus of animals are other examples of the ability to produce disease by the transfer of tissue materials from one animal to another.

Hindle and Stevenson[9] (1932) found inclusion bodies almost invariably in the kidneys of London sewer rats. In rats obtained in other localities, such inclusion bodies were found only in the kidneys of the rats which presumably might have lived in sewers or fed on town refuse since they were absent from rats caught in the country under hay stacks, or in similar localities. Inclusions were never found in white rats, including both normal individuals and others infected with various diseases, or exposed to the action of kidney irritants. The inoculation of suspensions of the kidneys from sewer rats resulted in disease in white rats. Acidophil intranuclear bodies were produced in the kidneys also by the injection of Berkefeld filtrates of the material.

The writers suggest that a virus, responsible for the inclusion bodies in the kidneys of the sewer rats, was present in sewage. It appears highly probable, however, that a toxic substance in the sewage, rather than a virus, may explain the reaction in the kidneys. This possibility appears to be indicated as a result of the observations that have been made by Pappenheimer and Maechling[10] (1934). These workers found, following the intramuscular injection of 0.4 Gm. of bismuth in the form of bismuth campho-carbolic acid in olice oil (bismocymol), into a syphilitic patient, that a tubular nephritis of moderate intensity resulted, with regenerative change in progress at the time of the patient's death from a metastasizing gastric carcinoma. There were refractile spherical bodies within the nuclei and cytoplasm of the renal epithelial cells of the convoluted tubules. A second case in which a patient had been given 1 Gm. of potassium bismuth tartrate suspended in peanut oil was found to have similar refractile globules in the epithelium of the renal tubules. The histological reactions in the two cases were identical.

A white rat was injected intramuscularly with successive doses of bismocymol. The kidney was found to be the site of an intense tubular necrosis. Spherical inclusion, identical with those in the human tissue, were present within the nucleus and cytoplasm. They gave similar microchemical reactions. The experiment was repeated on seven other rats. The inclusions were found in five out of the seven rats, in all of those surviving more than four days.

Pappenheimer and Maechling concluded that since similar intracellular bodies are not formed at the site of the injection and cannot be detected within the glomeruli, one can assume that the material of which they are composed is eliminated from the glomerulus either in solution or in finely dispersed form, reabsorbed by the tubules, and segregated by the nucleus in the form of one or rarely two refractile globules.

Cowdry and Scott[11] (1935) observed inclusions in the kidneys of twelve out of sixteen macacus monkeys which had been treated with irradiated ergosterol. An examination of the kidneys of ten normal controls showed intranuclear inclusions in only one, an incidence of 10 per cent as compared with 75 per cent in the monkeys treated with irradiated ergosterol. Kidney inclusion bodies were found in 16 out of 85 (18.8 per cent) cases of experimental poliomyelitis, many of which were killed before severe symptoms ensued. Two out of four monkeys dying from unknown causes showed kidney inclusions. There were no inclusions in the kidneys of eighteen monkeys which died of a variety of diseases, including acute diarrhea, rabies, meningitis, tuberculosis, and pneumonia, nor in a monkey injected with measles blood.

Syverton and Larson[12] (1947) studied the kidneys of 139 wild rats collected in widely scattered areas, viz, Rochester, upstate New York, San Francisco waterfront, and Denver. The wild rats whose kidneys contained many inclusion bodies were indistinguishable on gross inspection

from rats whose kidneys contained no inclusion bodies. It was noted however, that inclusion bodies were absent from immature rats that were less than half grown and from rats captured on farms. Only rarely were rats found that were not well nourished and in excellent physical condition. From these observations, the writers observe that if the inclusion bodies were associated with an infection, the infection was inapparent. Since the inclusion bodies were found largely in the kidneys of rats captured near sewers and dumps, it was considered possible that a toxic agent, e. g. a metal, might have been ingested and absorbed from the gastro-intestinal tract, to produce changes in the renal epithelial cells during excretion. Repeated ingestion of some toxic agent, perhaps some heavy metal was suggested by the fact that the inclusions were limited to urban rats; that the incidence of occurrence and the number of inclusion bodies increased with age; and, moreover, that rats captured in refuse dumps or downtown showed more evidence of inclusions than suburban rats.

Dalldorf and Williams[14] (1945), during nutrition studies, observed that many of their rats showed evidence of lead poisoning. In the histological preparations, large acidophilic inclusion bodies were found to be numerous in the epithelium of the convoluted tubules of every animal examined. The source of the lead was found to be certain concealed babbited bearings of the food masticator used in the mixing of the rations. The food did not contact these bearings, but small variable amounts of lubricating grease, heavily charged with lead, exuded occasionally through crevices at the ends of the blades into the mixing chambers.

Blackman[14] (1936) found intranuclear inclusion bodies in the tubular epithelium of the kidney and in the liver cells of 21 children dying from the effects of acute lead poisoning and lead encephalitis. No clinical evidence was found in any of the children, however, which would indicate appreciable impairment of the function of the kidneys.

Blackman gave daily a few cc. of a 10 per cent suspension of lead carbonate in water mixed with food to 24 young white rats. Typical inclusion bodies were found microscopically in the kidneys of 20 of 24 rats and were present in the liver cells of 8 rats. Blackman states regarding the inclusion bodies, "It seems probably that the acidophilic intranuclear bodies which appear in some diseases represent nothing more specific than abnormal nuclear material and it is clear that they may be caused by factors other than infection with filtrable viruses."

Findlay[15] (1932) found intranuclear inclusions in liver cells of mice (Chacton strain) and he was able to transfer them by inoculation of Berkefeld filtrates to the liver cells of other mice. Among the possible explanations for the presence of the inclusion bodies, Findlay suggested that they represent a metabolic disorder of the affected cells. He points out that the mice were in no way abnormal except for the inclusion bodies and that if the changes are due to mutation such changes are not present at birth, nor has it been possible to find any record of a mutation affecting the nucleoli of any one organ. He says that it would seem to be premature to assert that

the presence of the inclusions invariably denotes infection by an ultramicroscopic virus.

Cowdry, Lucas, and Fox[16] (1935) reported the result of a search for nuclear inclusions in kidney specimens from 1012 human autopsies. Inclusions were found in 17 kidneys or 1.67 per cent as contrasted with 14 of 163 animals or 8.58 per cent.

Lucas[17] (1947) found intranuclear inclusions in the cells of the islands of Langerhans of nearly all White Leghorn chickens over 30 days of age.) "If the inclusion bodies do signify the presence of a virus," he says, "it must be latent, since inclusions are present in some birds which to all appearances are normal and healthy, . . . If the inclusion bodies are not associated with a virus, then it is possible that they have some, as yet unknown, connection with physiological activities in the islet tissue."

Submaxillary Gland Virus and Inclusion Bodies

Unusual changes in the submaxillary glands of guinea pigs were first described by Jackson[18] (1920). The inclusions were found in 26 of 48 pigs examined and they were interpreted as protozoa probably coccidia.

Cole and Kuttner[19] (1926) found these peculiar cells present in the submaxillary glands of 84 per cent of guinea pigs over six months of age; in very young guinea pigs they were present only occasionally.

They injected submaxillary gland material from older guinea pigs into the submaxillary glands of young ones, free from infection, and the pigs were killed in varying intervals from 2 to 12 days following the injections. Sections were made from the submaxillary glands. In nine out of eleven injected glands, a marked mononuclear reaction involving the interstitial tissue was present. In certain areas cells were found which showed nuclear changes with acidophilic inclusions, exactly resembling those seen in lesions of herpes simplex and allied conditions.

A suspension of sumaxillary glands were injected into other locations where similar inclusions do not occur. The most striking results were obtained when the injections were made into the brain. On about the fifth day the animals died. The brain showed no gross abnormalities beyond congestion. There was a well marked exudate over its surface including the cerebellum. The exudate consisted of mononuclear cells, lymphocytes, and large cells with vesicular nuclei. In this meningeal exudate there was a large number of cells, each of which contained an acidophilic mass within the nucleus. These cells resembled in all particulars the cells containing nuclear inclusion bodies which occur in herpes simplex and related conditions.

The transmissible agent of the submaxillary gland was destroyed by heating at 50° F. for one hour; it was not injured by preservation in 50% glycerol; and it passed through a Berkefeld N filter.

Kuttner[20] (1927) points out that the demonstrable lesions in the submaxillary glands of guinea pigs can be demonstrated 12 to 15 days

after injection of the submaxillary gland material. When such a reaction is produced, the guinea pigs are refractory to intracranial inoculation. When the active principle in the submaxillary glands is inactivated by heat, no lesion develops in the submaxillary glands of young guinea pigs following subcutaneous inoculations. In cases in which the submaxillary glands were removed, subcutaneous injection of the active principle of the submaxillary gland localized in the parotid gland, and the animals became refractory to intracerebral inoculation.

Kuttner recorded that brain transmission was accomplished when massive doses or multiple injections were used. The active agent was transmitted continuously from skin to submaxillary gland through a series of seven animals.

Scott[21] (1929) found that if the submaxillary duct of guinea pigs was ligated, the formation of inclusions could be completely inhibited, but there was heightened physiological activity in the opposite side. The result of this experiment came as a surprise to Scott since, as he points out, the operation causes injury and the active formation of young cells, two factors which are believed by Rivers[22] and others to be influential in the promotion of virus activity.

Scott found, conversely, that the development of inclusions may be greatly aided by the stimulation of the submaxillary gland by pilocarpine. The high degree of functional activity in this case is maintained to a stage of profound exhaustion of the gland.

Andrews[23] (1930) found that guinea pigs with inclusion bodies in the salivary glands had neutralizing properties in their blood serum.

Hudson and Markham[24] (1932) were able to carry out serial transmission from brain to brain in young guinea pigs. It was effected in two series, in one to the second generation and in the other to the third. The histopathology was that of a meningoencephalitis. The inflammatory reaction irregularly involved the meninges, the underlying brain substance, and the perivascular tissue of the meninges. When sufficient time (15 days or more) elapsed between cerebral inoculation and death, typical cellular inclusions were seen in the salivary glands, whereas none was found in animals that died earlier (7 to 9 days).

Thompson[25] (1932) examined 70 two months old rats comprising a consecutive series during the months of October and November for inclusion bodies. The highest incidence was noted in the first quarter. In the last half, affected glands occurred sporadically. These observations suggested a seasonal variation and that the occurrence of the inclusions might be an epizootic condition. It was considered possible that in view of the high percentage of inclusion bodies in the submaxillary glands of adult guinea pigs that the adults might have served as a reservoir. Therefore twelve rats over six months of age, which had been used as breeders, were examined. The results were negative.

Rector and Rector[26] (1934) examined the submaxillary glands of 14 moles and found inclusion bodies in the submaxillary glands of all of them. In none of the moles were there definite clinical symptoms. They state, "The inclusions in the salivary glands of moles are sufficiently like those of humans, guinea pigs, and rats to suggest a more or less common origin."

Kuttner and T'Sun T'Ung[27] (1935) pointed out that no matter where the submaxillary virus is injected, it localizes in the salivary glands and produces typical pathological lesions. "The occurrence of the virus in the kidney of animals which had been inoculated intracerebrally seemed to indicate that the submaxillary gland virus might be eliminated through the kidney or that it might possibly localize in the epithelium of the kidney as well as in the submaxillary gland. In order to obtain a wide distribution, it is obvious that the blood of the animals which had been inoculated subcutaneously must have at some time contained the virus but apparently these viruses do not persist in the circulation."

Cowdry and Scott[28] (1936) found inclusion bodies in the salivary glands in cebus fatuellus, but not in rhesus monkeys, resembling those in the salivary glands of the guinea pig, rat, mouse, and hamster. The animals in this study were at least three years old.

McCordock and Smith[29] (1936), after subcutaneous inoculations of submaxillary gland material, were able to produce intranuclear inclusion bodies in the pancreas of mice in addition to the usual salivary gland lesion. Visceral lesions involving the liver, kidneys, intestine and pancreas resulted from intraperitoneal injections.

Rector[30] (1936), in a series of 120 wild rats collected at 16 different locations in St. Louis, all of which were trapped or shot in rubbish heaps, except eight that were captured at a meat packing plant, found nuclear inclusions in both the submaxillary glands and kidneys of 24 animals, and in the kidneys alone in 84.

Markham[31] (1938) suspected that the presence of inclusions in organs such as the salivary glands and kidneys of animals might indicate that their secretions may be infectious. He was unable to infect young guinea pigs by intracerebral inoculations using Berkefeld N filtrates of urine and saliva. Two weeks after the injections, histological examination of the brain, salivary glands, and kidneys revealed no characteristic lesions.

"Inclusion Disease" In Infants and Children

The history of nuclear inclusions in infants and children dates back to observations made by Jesionek and Kiolomenoglou[32] (1904). They reported the finding of protozoan-like structures in the kidneys, lungs, and liver of an eight months old syphilitic stillborn fetus.

Shortly after the publication of this paper, Ribbert[33] (1904) recalled that he had seen similar bodies some twenty years previously in the kidneys of a syphilitic newborn and the parotid glands of children.

Loewenstein[24] (1907), at Ribbert's suggestion, studied the parotids of thirty children from two months to two years and found inclusions in four.

Pisano[25] (1910) reported the finding of similar inclusion bodies in the tissues of a stillborn fetus. The viscera in this case showed pronounced lesions. In the liver there was gummatous hepatitis while the kidneys, spleen, thyroid and lungs were all the seat of interstitial fibrosis. The inclusions were present in large numbers in the kidney, fairly numerous in the liver, and rare in the lungs.

Pisano, as well as Perrando[26] (1912) considered the inclusions to be epithelial in origin but "arrested in their development by the dystrophic and paraplastic effect of the syphilitic infection."

Mourchet[27] (1911) described inclusions in the bile ducts of an eight day old syphilitic infant with jaundice.

Smith and Weidman[28] (1911), in a paper entitled, "Infection of a Stillborn Infant by an Amebiform Protozoan (Entameba Mortmatalium)", described the same bodies that the previous writers had reported. The supposed parasites in the liver and kidneys were surrounded by a definite inflammatory reaction of lymphoid and polymorphonuclear leucocytes. In 1914, these authors[29] reported a case suspected to be syphilitic in which similar inclusion bodies were found.

Goodpasture and Talbott[40] (1921) published a paper, "Concerning the Nature of the Protozoan-like Cells in Certain Lesions of Infancy." They found acidophilic intranuclear bodies in the alveoli of the lungs, bronchi, and in the glomeruli of the kidneys in a six weeks old male infant who had green stools from birth, glucose in the urine, edema of the feet, and cough. The writers noted the resemblance of the inclusion bodies to those described by Tyzzer[41] (1906) in varicella. They felt certain that they were not protozoa. "The peculiar change is a retrograde one," Goodpasture and Talbott state, "by which certain cells become independent of the body tissues and capable perhaps of wandering about." They suggested the term "cytomegalia" to emphasize the enlargement of the cells.

De Lange[42] (1922) found inclusion bodies in a three day old icteric infant with cirrhosis of the liver. The inclusions were found in the convoluted tubules of the kidneys; in their vicinity, there was round cell infiltration of the stroma. They were interpreted as some undetermined form of cell degeneration.

Müller[43] (1922) reported three cases in which inclusions were found only in the kidneys, one in a stillborn, one in a child 8 weeks old with hydrocephalus and slight interstitial nephritis, and the third in a two weeks old child with congenital syphilis.

Müller excludes the possibility of protozoa because of their occurrence in stillborn infants, and because it did not seem possible that they could have passed the placental barrier. He considered the inclusions to have originated from tissue cells which had undergone a peculiar degeneration.

Lipschütz[44] (1921) discovered that similar structures are constantly and characteristically associated with lesions produced by the herpes virus in man and in rabbits. He interpreted them as the expression or result of an intranuclear virus.

Jackson[45] (1922) found inclusion bodies in the kidneys of a fifteen months old child who died suddenly in a convulsion. Neither the gross nor histologic examination of the tissues revealed any other apparently sufficient cause of death. One might speculate whether or not this case may have been the result of acute poisoning.

Wilson and Dubois[46] (1923) found nuclear inclusions in the epithelial lining of the ducts of the parotid and submaxillary glands in a fatal case of keratomalacia. The case was a five months old baby girl who for a long period of time had been fed condensed milk, a food deficient in fat and protein and necessarily low in vitamin A.

Walz[47] (1926) observed inclusions in the pancreas, as well as in the kidneys, liver, lungs, and thyroid of a newborn infant.

Wagner[48] (1930) noted inclusions in the lungs, kidneys, liver, pancreas, thyroid, epididymis, and sublingual gland of a two weeks old premature infant, in whom no evidence of congenital syphilis could be found. He also found inclusions in the parotid glands of four of a small series of infants.

Farber and Wolbach[49] (1932) studied the submaxillary glands of 183 infants that came to autopsy. They found large cells containing intranuclear and cytoplasmic inclusion bodies ("protozoan-like bodies") in 22 cases (12 per cent). There were no findings that would justify the grouping of these cases into a single, or even homogenous, clinical or pathological class. The outstanding features common to most of the group was hyperpyrexia and acute infection somewhere in the body. An adequate cause for death was found in every case. The clinical signs and symptoms were all satisfactorily explained by the clinical and postmortem findings.

The authors state, "The fact that 80 per cent of the cases occurred in individuals under one year of age, that is, during a period when known diseases associated with a filtrable virus are rare, is of more than passing interest."

Vidari[50] (1940) reported a case with "protozoan-like cells" in the lungs, thyroid, liver, and kidneys, associated with icterus neonatorum and erythroblastosis. He states that there are five similar cases in the literature.

Kinney[51] (1942) found intranuclear inclusions in the lungs of four, and in the salivary glands in two autopsies in infants suffering from clinical whooping cough.

Intranuclear inclusions similar to those of herpes were described in the brain of a three year old child. This patient's illness dated from a fall on July 1, 1933, from a coaster wagon in which he received a severe blow in the lumbar region. There was no evidence of injury except for a bruise. Two days later the child fell from a porch and cried for a considerable length of time. On July 9, the child had a convulsion, trembling and crying for

short intervals. Three days later there were more convulsions. The child was admitted to the hospital and died two days later. At autopsy no gross changes were observed.

A second patient, a female premature infant, 14 days old, developed diarrhea on the eleventh day and on the following day vomited and refused food. Jaundice was noticed and occult blood was found in the stools. She became dehydrated and moribund despite supportive treatment and died on the 14th day. At autopsy, inclusions typical of those in the salivary glands of infants and guinea pigs were found in the brain, kidneys, pancreas, lungs, and liver.

Poliomyelitis Virus and Inclusion Bodies in Non-Specific Diseases

Stewart and Rhodes[52] (1929) reported the discovery of intranuclear inclusions in the cells of the nasal mucous membrane of monkeys (macaca rhesus) inoculated with the virus of poliomyelitis. Since they were found occasionally in control monkeys, they did not attach any particular significance to them.

Covell[53] (1930) found certain nuclear changes in the ventral horn cells and the cells of the medulla in poliomyelitis. These were noted to follow or occur spontaneously with the more easily recognized cytoplasmic degeneration which was often profound. Inclusions were found shortly after the onset of the paralysis (1 to 3 weeks) and were observed only in cells undergoing marked degeneration.

Hurst[54] (1931) confirmed Covell's findings in 25 out of 28 cases of experimental poliomyelitis in monkeys. He found similar inclusions in the spinal cord of one human case. Inclusions were not found in monkeys which lived for six days, one month, and one year, respectively, after the initial paralysis. The examinination of 24 controls including normal animals and those with other pathological conditions was entirely negative. The inclusions appeared always in cells undergoing degeneration. Their number was greater in the early stages of the disease and on the first day of the paralysis. A week later they were much less numerous.

Covell[55] (1932) observed similar lesions in experimental poliomyelitis, not only in the nasal mucosa but in the epithelial cells of the trachea, lung, and bile ducts. The inclusions were found in 20 out of 60 monkeys and their distribution was patchy. They were likewise occasionally seen in animals which had not been subjected to the virus of poliomyelitis.

Wolff and Orton[56] (1932), in studying material from two cases of acute anterior poliomyelitis, found inclusions in the ganglion cells of the spinal cord and medulla in both cases. The ganglion cells containing the inclusions showed marked chromatolysis and some satellitesis, but no neurophagia or other signs of advanced degeneration.

These writers used control material from the central nervous systems of 25 other patients who came to autopsy as a result of various diseases. In 20 of these cases the essential disease process was in the central nervous system and in five in the body organs. Intranuclear inclusions similar to

those seen in the poliomyelitis cases were found in all of these, either in the medulla or pons, less frequently in the cortex, basal ganglia, and spinal cord. They were present in approximately the same numbers as in poliomyelitis cases and resembled in all essential features the inclusions seen there.

The control cases examined by the writers included: toxemia of pregnancy, tuberculous meningitis, myasthenia gravis, chronic basilar meningitis, tetanus, acute suppurative leptomeningitis, chronic epidemic encephalitis, meningeal fibrolastoma, pernicious anemia, dissecting aneurism, chronic pulmonary tuberculosis, cerebral epidermoid, suppurative thrombophlebitis of uterus and pelvic veins, aneurism of right anterior cerebral artery (ruptured) spongioblastoma multiforme, meningeal fibroblastoma, and protoplasmic astrocytoma.

In a subsequent study, Wolff and Orton[57] (1933) reported that they had found inclusion bodies similar to those of poliomyelitis in 25 of 100 tumors of neuroectodermal origin, and in 15 out of 60 intracranial tumors of mesodermal origin. They quote Russell[58] (1932) who found inclusions in a third of a series of 192 gliomas that were examined, as well as Wolff[59] (1907) who described inclusions, chiefly cytoplasmic, in neoplasms.

Experimental Production of Inclusion Bodies

Goldschneider and Flatau[60] (1897) observed structural changes in the anterior horn cells in animals heated to 107.6° and up to 111.2° F. This could indicate that this alteration is due to some physiochemical reaction and not directly due to heat since similar changes did not occur when these tissues were heated post-mortem at higher temperatures.

Neuropathological changes were observed in the brain of animals in experimental heat-stroke by Freeman[61] and in the brain and spinal cord in heat-stroke in humans by van Gieson[62] which are suggestive of those found in poliomyelitis. Freeman attributed the changes in the cytoplasm and nucleus to hydroptic degeneration and van Gieson concluded that they were the result of a poison.

Hembacker and O'Leary[63] (1930) showed that repetitive stimulation by electricity of the axon brings about granulation of the chromatin and its clumping about the nucleolus. The chromatin mass resembled the nuclear inclusions which have been considered pathognomonic of several virus infections.

The nuclear change described was observed: in the autonomic ganglia following pre- and post-ganglionic stimulation, in spinal ganglia after stimulation of the dorsal root, in the anterior horn cells following stimulation of the cord, and in the ganglion cells of the heart following stimulation of the vagus.

Davenport et al[64] (1931) found that nuclear inclusions occurred with great regularity in extirpated ganglia in hypertonic solutions. The phenomenon of nuclear changes in these experiments suggested to these workers that the nuclear inclusions observed pathologically may be the result of disturbed osmotic conditions in the cells.

Lee[65] (1933) observed nuclear changes following the intravenous injection of various solutions.

When 60 cc. of a 50 per cent solution of glucose per kilo of body weight was injected slowly during one hour and the animal was killed immediately, marked changes were observed in the nuclei of the spinal cord, anterior horns and Purkinje cells. The nuclear chromatin, dispersed in reticular fashion in the cells of normal controls, formed a compact mass about the nucleolus and was separated from the nuclear membrane by a halo. The nucleolus was noticably vacuolated and swollen. The only cytoplasmic alteration was noted in the ganglion cells; here a varying degree of central chromatolysis was apparent. Animals, of like weight, when killed three hours after the injection of a similar quantity of glucose showed less obvious nuclear changes, indicating a return to normal.

After the injection into three animals of 150 cc. of a 30 per cent solution of sodium chloride over a period of 45 minutes, they were killed immediately. Lesions were found in the Purkinje, anterior horn, and spinal ganglion cells which showed changes similar to those seen in glucose injected animals. The chromatin, however, was more acidophilic and less concentrated about the nucleolus.

In four animals killed following the injection of from 300 to 400 cc. of distilled water in one hour and 15 minutes, intranuclear bodies were observed which simulated those described by Covell[58] (1930) in the nerve cells of acute anterior poliomyelitis.

Salyrgan was injected intramuscularly into six cats in ½ cc. doses daily for four days and intravenously into four cats in 1 cc. doses daily for five days. The animals were sacrificed at graded intervals. Nuclear changes were observed in all of the first group but in none in the second, nor in 35 control cats not subjected to this treatment but employed in the laboratory for other experiments. The inclusions occurred in the pancreas of six animals, kidneys of three, testes of two, and adrenal of two. They were absent from the nervous system.

Cox and Olitsky[66] (1934), in studies on the prevention of experimental equine encephalitis in guinea pigs by means of virus adsorbed on aluminum hydroxide, observed intranuclear inclusion bodies characteristic of encephalitis virus infection in the phagocytic mononuclear and giant cells of the induced subcutaneous nodules. When the chemical alone, free from the virus, was introduced under the skin of guinea pigs, similar inclusions were seen in the resulting foreign body reaction.

It appears to be significant in this connection that encephalitis has been produced by tetanus and diphtheria toxoids. "Histological changes similar to those seen in infective encephalitis may be produced by carbon monoxide poisoning, brain injury, arteriosclerosis, uremia, pregnancy toxemia, and toxic agents like alcohol and lead."[67]

Lee[68] (1936) produced Type B inclusion bodies in the cells of the anterior horn by intravenous injection of distilled water, Hypertonic glucose, glucose plus acacia, saline solution, as well as sodium bicarbonate solution,

resulted in the production of Type A inclusions in Purkinje cells, anterior horns, spinal and sympathetic ganglia, and pyramidal cells.

Olitsky and Harford[69] (1937) were able to produce inclusion bodies, indistinguishable from those observed in virus infections, by the injection of aluminum compounds, ferric hydroxide, and carbon. Intranuclear inclusions, similar to those described, were seen in subcutaneous nodules induced in guinea pigs by injection of brain tissue derived from apparently normal animals.

Olitsky and Harford[70] (1938) injected autoclaved materials subcutaneously into guinea pigs and they subsequently removed nodules so produced for histological examination. When aluminum hydroxide or alundum was used, intranuclear inclusion bodies were always found in the mononuclear and giant phagocytic cells of the tissue reaction about a week after the injection or usually as long as the nodules persisted. Inclusion bodies were found regularly and in small numbers with ferric hydroxide and carbon. Histological reactions and morphological characteristics of such inclusions resembled very closely those of viral diseases.

A list of additional materials which were similarly injected subcutaneously into guinea pigs in order to determine whether the resulting tissue reactions would also produce inclusion bodies included: suspensions of normal brain tissue of mice, guinea pigs, and rabbits (fresh or autoclaved); normal rabbit tissues (liver, spleen, kidney, testicle); commercial lecithin; alcoholic extract (lipins) of monkey brain; phosphatide of tubercle bacilli; and 1:2:5:6 dibenzanthracene. Although reactions to these substances differed somewhat from one another and from that of aluminum hydroxide, they all contained mononuclear phagocytic cells, and in certain instances also contained giant phagocytic cells. Brain tissue, of all the material tested, gave reactions containing intranuclear inclusions. The occurrence of the inclusions was noted with rabbit and guinea pig brain, fresh or autoclaved, injected into guinea pigs, but not with mouse brains.

Birch and Lucas[71] (1942) employed the technic of Olitsky and Harford using aluminum oxide, ferric hydroxide, and carbon. They produced inclusion bodies consistently with aluminum oxide. The best results were obtained when the subcutaneous nodules were removed 17 to 23 days after injection of the material. Their work confirmed that of Olitsky and Harford who considered the inclusions were indentical to those found in various virus infections.

Herpes Zoster and Herpes Simplex

Several writers have indicated that the various herpetic lesions result from a toxin. Robinson and Hirschler,[72] for example, state, "It is highly probable that the vast majority of all cases of herpes of the various types are the result of the action of a toxin."

Herpes zoster, first described by Head[73] as acute posterior poliomyelitis, is strikingly similar in its epidemiology, symptomatology, and pathology to

acute anterior poliomyelitis. Head pointed out that herpes zoster is an acute specific disease of the nervous system analogous to acute anterior poliomyelitis.

Garrow[74] observed during August and September, 1911, when acute anterior poliomyelitis was epidemic in Maryport, England, that there was also prevalent an unusual number of cases of herpes zoster. He felt that there was an etiological connection between the diseases and pointed out facts to support this idea in a paper entitled, "Are Polio and Herpes Zoster the Same Disease?"

Several writers have observed that herpes zoster may occur at any age, but that it is seen most frequently in children and young adults. This fact, and the observations that herpes zoster occurs chiefly in males, corresponds with similar observations in poliomyelitis. There is also a corresponding relationship in the seasons in which each of these diseases occurs.

Herpes zoster may result from chemical poisons, non-specific bacterial toxins, traumatism, and pressure on the spinal cord.

It has followed poisoning by arsenic, carbon monoxide, gold, mercury, chaulmoogra oil, tuberculin, alcohol, as well as other poisons. Epidemics of herpes zoster have followed the ingestion of arsenic in beer in England. Levit and Luppi[75] described cases of herpes zoster with alcoholic polyneuritis. Caspers[76] reported cases of polyneuritis and herpes zoster as late sequels of acute phenobarbital poisoning.

The toxins resulting from a variety of infections, including typhoid fever, pneumonia, tuberculosis, malaria, and cerebrospinal meningitis, have resulted in the production of herpes zoster.

An attack of herpes zoster, like poliomyelitis, commonly begins with fever, malaise, anorexia and gastro-intestinal disturbances. There is hyperaesthesia and there may be headache. There may be evidence of meningeal irritation in herpes zoster, as in poliomyelitis, and a lymphopleocytosis with increased protein in the spinal fluid.

The simultaneous occurrence of herpes zoster and poliomyelitis has been noted.[77] Taterka and O'Sullivan[78] (1943), in reviewing the literature on paralytic manifestations in herpes zoster, found that the eruption preceded the paralysis in about three-fourths of the cases, and that it followed in one-fourth.

Parkinson[79] (1948) points out that in some cases of herpes zoster in which motor symptoms occur that the anterior horn cells of the spinal cord are affected in a manner similar to that in poliomyelitis. Head,[73] Osler and McCrae,[80] and others, have pointed out that the pathology of herpes zoster is analogous to acute posterior poliomyelitis.

It has been found that herpes zoster, like poliomyelitis, rarely occurs twice in the same individual.

Herpes Simplex may result from mechanical irritation such as cold winds, solar rays, sea air, and local traumatism.

It can follow the ingestion of alcohol, arsenic, benzol, arsenobenzol, mercury, or the inhalation of ether, among other poisons. Van Rooyen[81] (1947) noted its appearance after sulfapyradine therapy. Herpes simplex has followed the injection of vaccines, milk, and colloidal metals.

Gastro-intestinal disturbances from the ingestion of certain foods as well as from autointoxication have been held responsible. Herpes simplex has been noted to result from nervous and emotional disturbances.

Bactero-toxins from non-specific infections have been found to cause herpes simplex. These include respiratory infections, such as common colds, bronchitis, and pneumonia, exanthemata, cerebrospinal fever, influenza, typhoid fever, and paratyphoid fever.

Artificial fever has not infrequently caused herpes simplex. It has been observed in some women at or near the menstrual period.

Herpes simplex is frequent in childhood; epidemics have been observed.

Inclusion bodies are found in the herpetic vesicles and a filtrable virus can be recovered from the vesicle fluid. This transmissible agent has been found in the saliva both in patients with herpes and in normal persons. Encephalitis can be produced when it is injected intracerebrally into animals, and a keratitis results from injection into the cornea.

These experiments appear to be of academic interest only as there seems to be no relation between herpes encephalitis thus produced and epidemic encephalitis. Goodpasture[82] (1929) states regarding this fact, "The problem of the etiology of epidemic encephalitis is still unsolved, and at the present time there does not seem to me to be any convincing evidence that it is caused by the herpetic virus."

An interrelationship between the herpes virus and the poliomyelitis virus appears to exist as shown by observations made by Weyer.[83] He showed that children who carried no antiviral substances in their sera for poliomyelitis likewise were devoid of antiviral substances toward the herpes virus. "Herpes virus neutralizing properties have been discovered in the blood of monkeys which have reacted to poliomyelitis virus."

Comment

The material that has been presented in this report indicates that tissue reactions with the formation of "viruses" and inclusion bodies can result from toxic substances. The significant fact that inclusion bodies in many of these cases were found in the nasal mucosa, parotid and submaxillary glands, liver and bile ducts, pancreas, kidneys, and lungs would appear to indicate that toxic substances may be carried to these localities for excretion and that local reactions, including the production of a "virus," results from the toxic stimulation of these tissues.

Observations made by Toomey[84–85] would appear to indicate that a toxic substance, as suggested, is excreted from patients with poliomyelitis. He demonstrated a toxic factor in the stools and urine in cases of human

poliomyelitis. It was found also in the intestines of monkeys ill with experimental poliomyelitis but not in those of normal animals.

The injection of a stool emulsion or urine from human cases of poliomyelitis into guinea pigs produced toxic reactions and death. It was found that there were changes in the spinal cord, resembling those of poliomyelitis, when stool emulsions from poliomyelitis patients were injected into rabbits.

Emulsions made from the spinal cords of animals that died after the subcutaneous injections of stool emulsions could be carried in series through other animals. A sterile eluate was about as toxic as the emulsion of whole stool which contained intestinal bacteria. Poliomyelitis convalescent serum protected guinea pigs against the toxic symptoms caused by the stool emulsion.

The discovery by Gard[89] that intestinal material from normal humans can not be distinguished from virus protein suggested tentatively that intestinal protein is an avirulent or non-neurotrophic varient of poliomyelitis virus, which, under the influence of exogenous factors, may undergo variation to a neurotrophic form. This work, and the observations of Toomey which are mentioned above, suggest that the poliomyelitis virus that is found in human feces and subsequently in sewage, is an intestinal protein that is "activated" by exogenous and endogenous poisons in a manner similar to the formation of the submaxillary gland virus of animals and the herpes virus of man.

Early poliomyelitis investigations, before the discovery of the so-called virus of poliomyelitis, showed that it was possible to produce the disease by the injection of a variety of organisms. Non-specific bacterial toxins, as pointed out, can also result in the development of herpes zoster and herpes simplex. These facts doubtless can be correlated with observations made by Vaughan et al.[90] They state that the poison elaborated in all infectious diseases is the same.

Boycott[91] (1929) asks significantly regarding viruses, "Is the agent the cause of the disease or is the disease the cause of the agent?" Regarding experimental procedures with viruses, he says, "We put in so much virus and we get out more; we have no evidence, nor, I think the right to assume, that the particles which we get out are the direct descendants of those we put in."

Some scientists consider the virus of herpes, poliomyelitis, and certain other so-called viruses, to be living infectious agents and diseases in which they are found to be infectious and communicable. Direct proof of this relationship in humans is lacking.

Other scientists have suggested that the herpes virus, and presumably other so-called viruses, including the poliomyelitis virus also, may be a transmissible ferment or non-living toxic substance which so acts upon cells as to cause multiplication of the same ferment or toxic substance and they imply that it may arise spontaneously under certain conditions.

This latter explanation appears to be nearer the truth. As has been shown in this report, viruses and inclusion bodies, can be produced within the body as a result of toxins, and it is possible to experimentally transmit viruses thus produced to other animals.

Although the submaxillary gland virus of animals, as well as the so-called virus of human poliomyelitis, can be injected into experimental animals to produce disease, there is no evidence that these "viruses" are not the result of a toxic substance in the food and water of the animal in the one case, and of the human in the other. It would appear, therefore, that transfer experiments, isolation of various "strains," purification, and ultramicroscopic photographs of these "viruses" would seemingly be merely of academic interest. The failure of the virus theory of poliomyelitis—after forty years of research—to explain the pathogenesis of the disease would indicate that another factor is responsible.

The solution to the problem of poliomyelitis, therefore, would appear to be found in the presence of a toxic substance in food and water which would presumably be present in areas and during seasons where epidemics of poliomyelitis appear. The search for such a toxic substance as the primary cause of the disease, instead of prolonged seeking for the product (virus) of the disease would more probably result in prevention and successful treatment. The fundamental principles of therapy of poliomyelitis, therefore, would follow logically the prevention of the poisoning responsible for the "virus," detoxification of the body, and correction of the pathological physiology resulting from the poisoning.

Summary

1. The term "virus infection" has been applied, without justification, to a number of human, animal, and plant diseases. It is applied not only to certain diseases because a transmissible agent in the tissues can produce a similar disease in experimental animals, but it has also been loosely employed to explain the etiology of a disease when a bacterial etiology cannot be demonstrated.

2. It is shown in this report that "viruses" and nuclear inclusions can be produced in the body as a result of toxic substances that are introduced into the body.

3. It is noted that tissue reactions with the formation of "viruses" and inclusion bodies often occur in tissues involved in the excretion of poisons from the body.

4. The failure of the virus theory of poliomyelitis—after 40 years of research—is explained by the fact that the primary causative factor is a toxic substance which is present in food and water in areas and during seasons when poliomyelitis epidemics occur, and that the so-called virus of the disease is formed in the body as a result of the poisoning.

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REFERENCES

1. Scobey, R. R.: *Arch. Pediat.* 63:322–352, July 1946.
2. Scobey, R. R.: *Arch. Pediat.* 63:567–580, Nov. 1946.
3. Scobey, R. R.: *Arch. Pediat.* 64:132–143, March 1947
4. Scobey, R. R.: *Arch. Pediat.* 64:350–363, July 1947.
5. Scobey, R. R.: *Arch. Pediat.* 65:131–166, March 1948
6. Scobey, R. R.: *Arch. Pediat.* 66:476–495, Sept. 1948.
7. Johnson, J.: *Research Bull. No. 3*, Agri. Exp. Station, Univ. of Wisc.. 1935.
8. Landsteiner, K.: *Wien. klin. Wchnschr.* 21:1830–1908.
9. Hindle, E. and Stevenson, A. C.: *Nature* 129:796, May 26, 1932.
10. Pappenheimer, A. M. and Maechling, E. H.: *Am. J. Path.* 10:577–588 Sept., 1934.
11. Cowdry, E. V. and Scott, G. H.: *Am. J. Path.* 11:659–668, July 1935.
12. Syverton, J. T. and Larson, C. L.: *Arch. Path.* 43:541–552, June 1947.
13. Daildort, G. and Williams, R. R.: *Science* 102:668–670, Dec. 28, 1945.
14. Blackman, S. S. Jr.: *Bull.* Johns Hop. Univ. 58:384–404, 1936.
15. Findlay, G. M.: *Brit. J. Exp. Path.* 13:223–229, June 1932.
16. Cowdry, E. V., Lucas, A. M. and Fox, H.: *Am. J. Path.* 11:237–252, March 1935.
17. Lucas, A. M.: *Am. J. Path.* 23: 1005–1022, Nov. 1947.
18. Jackson, L.: *J. Infect. Dis.* 26:347–350, 1920.
19. Cole, R. and Kuttner, A. G.: *J. Exp. Med.* 44:855–873, Dec. 1, 1926.
20. Kuttner, A. G.: *J. Exp. Med.* 46:935–956, Dec. 1, 1927.
21. Scott, G. H.: *J. Exp. Med.* 49:229–236, Feb. 1, 1929.
22. Rivers, T. M.: "Filtrable Viruses." Baltimore, The Williams & Wilkins Co. 1928.
23. Andrewes, C. H.: *J. Exp. Path.* 11:23–34, Feb. 1930.
24. Hudson, N. P. and Markham, F. S.: *J. Exp. Med.* 55:405–415, March 1, 1932.
25. Thompson, M. J.: *J. Infect. Dis.* 50:162–170, 1932.
26. Rector, E. J. and Rector, L. E.: *Am. J. Path.* 10:629–636, Sept. 1934.
27. Kuttner, A. G. and T'Sun T'Ung: *J. Exp. Med.* 62:805–822, Dec. 1, 1935.
28. Cowdry, E. V. and Scott, G. H.: *Am. J. Path.* 11:647–655, July 1936.
29. McCordock, H. A. and Smith, M. G.: *Am. J. Path.* 63:303–310, March 1, 1936.
30. Rector, L. E.: *Proc. Soc. Exp. Biol. and Med.* 34:700–702, June 1936.
31. Markham, F. S.: *Am. J. Path.* 14:311–321, May 1938.
32. Jesionek and Kiolemenoglou: *Munch. med. Wchnschr.* 51:1905, 1904.
33. Ribbert, H.: *Centralb. f. Allg. Pathol. u. Path. Anat.*, 15:945, 1904.
34. Löwenstein, C.: *Centralbl. f. Allg. Pathol. u. Path. Anat.* 18:513 1907.
35. Pisano, C.: *Gazz. d. osp.* 31:249, 1910.
36. Perrando: *Pathologica* 4:310, 1912.
37. Mourchet, R.: *Arch. de Méd. Exp. et d'Anat. Path.* 23:115, 1911.
38. Smith, A. J. and Weidman, F. D.: *Univ. Pennsylvania M. Bull.* 23:285, 1910–1911.
39. Smith, A. J. and Weidman, F. D.: *Am. J. Trop. Dis.* 2:256, 1914–1915.
40. Goodpasture, E. W. and Talbott, F. B.: *Am. J. Dis. Child.* 21: 415–425, May 1921.
41. Tyzzer, E. E.: *J. Med. Res.* 14:361, 1906.
42. De Lange, C.: *Virch. Arch. f. Path. Anat.* 237:276, 1922.
43. Müller, J.: *Virch. Arch. f. Path. Anat.* 238:481, 1922.
44. Lipschütz, B.: *Arch. f. Dermat. u. Syph.* 136 428, 1921.
45. Jackson, L.: *J. Infect. Dis.* 30:636–642, 1922.
46. Wilson, J. R. and Dubois, R. O.: *Am. J. Dis. Child.* 26:431–446, Nov. 1923.
47. Walz: *Verhandl. d. Deutsch. Path. Gesellsch.* 21:236, 1926.
48. Wagner, H.: *Beitr. z. Path. Anat. u. z. Allg. Path.* 85:145, 1930.
49. Farber, S. and Wolbach, S. B.: *Am. J. Path.* 8:123–135, March 1932.
50. Vidari, E.: *Centralbl. f. Allg. Path. u. Path. Anat.* 76:161–166, 1940.
51. Kinney, T. D.: *Am. J. Path.* 18:799–807, Sept. 1942.
52. Stewart, F. W. and Rhodes, C. P.: *J. Exp. Med.* 49:959, 1929.
53. Covell, W. P.: *Proc. Soc. Exp. Biol. and Med.* 27:927–928, 1930.
54. Hurst, E. W.: *J. Path. and Bact.* 34:331, 1931.
55. Covell, W. P.: *Am. J. Path.* 8:151–156, March 1932.
56. Wolff, A. and Orton, S. T.: *Bull. Neurol. Instit. N. Y.* 2:194–209, July 1932.
57. Wolff, A. and Orton, S. T.: *Bull. Neurol. Instit. N. Y.* 3:113–123, June 1933.
58. Russell, D.: *J. Path. and Bacter.* 35:625, July 1932.
59. Wolff, J.: *Die Lehre Von der Krebskrankheit.* Gustav Fischer, Jena. 1907.
60. Goldschneider and Flatau: Quoted by Smith, E. E.: *U. S. Naval M. Bull.* 26:479–502, July 1928.
61. Freeman: Quoted by Smith, E. E.: *U. S. Naval M. Bull.* 26:479–502, July 1928.
62. Van Gieson, I. Quoted by Lambert, A.: *Med News* 71:97–109, July 24, 1897.

63 Heinbecker, P. and O'Leary, J. L.: *Anat. Rec.* 45:219, April 1930.
64 Davenport, H. A., Ranson, S. W. and Terwilliger, E. H.: *Anat. Rec.* 48:251–254, Feb. 1931.
65 Lee, J.: *Proc. Soc. Exp. Biol. and Med.* 31: 383–385, 1933.
66 Cox, and Olitsky, P. K.: *Science* 79: 459, 1934.
67 van Rooyen, C. E. and Rhodes, A. J.: "Virus Diseases of Man" 2nd Edit. New York. Thomas Nelson and Sons, 1948.
68 Lee, J.: *Am. J. Path.* 12:217, 1936.
69 Olitsky, P. K. and Harford, C. G.: *Am. J. Path.* 13:729–747, Sept. 1937.
70 Olitsky, P. K. and Harford, C. G.: *Proc. Soc. Exp. Biol. and Med.* 38:92–94, Feb. 1938.
71 Birch, F. M. and Lucas, A. M.: *Am. J. Path.* 18:1051–1058, Nov. 1942.
72 Robinson, W. F. and Hirschler, R.: Herpes Zoster and Herpes. *In Sajous' Analytic Cyclopedia of Practical Medicine* Vol. 5, pp. 498–519. Phila. F. A. Davis Co., 1925.
73 Head, H.: Herpes Zoster, in *Allbutt and Rolleston's System of Medicine* 9th Edit. Vol. VII, p. 473.
74 Garrow, R. P.: *Brit. M. J.* 1:621–622, March 18, 1911.
75 Levit, L. and Luppi, J.: *Rev. Med. de Rosario* 31:658–662, July 1941.
76 Caspers, J.: *Nervenartzt* 15:246–248, June 1942.
77 Fromenty, L.: *Gaz. hebd. d. sc. méd. de Bordeaux* 52:179, 1931.
78 Taterka, J. H. and O'Sullivan, M. E.: *J. A. M. A.*, 122:737–739, July 10, 1943.
79 Parkinson, T.: *Brit. M. J.* 1:8, Jan. 3, 1948.
80 Osler, Sir William and McCrae, T.: *The Principles and Practice of Medicine* 9th Edit. p. 1038, New York, D. Appleton & Co., 1923.
81 van Rooyen, C. E. Rhodes, A. J. and Ewing, A. C.: *Brit. M. M.* 2:298–301, Aug. 30, 1941.
82 Goodpasture, E. W.: *Medicine* 8:223–243, May 1929.
83 Weyer, E. R.: *Proc. Soc. Exp. Biol. and Med.* 30:309–313, Dec. 1932.
84 Toomey, J. A.: *J. Prev. Med.* 6:387, Sept. 1932.
85 Toomey, J. A.: *J. Prev. Med.* 6:379, Sept. 1932.
86 Toomey, J. A.: *J. Prev. Med.* 6:397, Sept. 1932.
87 Toomey, J. A.: *Am. J. Dis. Child.* 50:1173, Nov. 1935.
88 Toomey, J. A. and Takacs, W. S.: *Am. J. Dis. Child.* 61:35–40, Jan. 1941.
89 Gard, S.: Quoted by van Rooyen, C. E. and Rhodes, A. J., "Virus Diseases of Man." 2nd Edit. New York, Thomas Nelson & Sons, 1948.
90 Vaughan, V. C., Vaughan, V. C., Jr., and Vaughan, J. W.: "Protein Split Products in Relation to Immunity and Disease." Phila. Lea and Febiger, 1913.
91 Boycott, A. E.: *Ann. Rep. Smithsonian Institution* pp. 323–343, 1929.

Immunological Relationship of Poliomyelitis To Virus Enteritis

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The title of this paper might better be expressed as a question: "Is there a relationship between virus enteritis and poliomyelitis?" The author feels that the answer to this is very definitely yes, but as will be developed in this paper the answer is provisional rather than final.

This is a preliminary report of a concept that appears to have some sound reasoning behind it and which has some statistical support. The principal idea in this may require revision following adequate virus research on the problem.

The authors of this paper are orthopedic surgeons and not bacteriologists, but because of their specialty are quite interested in poliomyelitis from every standpoint. The personal element is being mentioned because it is largely responsible for the thought expended in regard to the thesis expressed in this paper. The senior author was born and reared in El Paso, Texas and has practiced orthopedics there for many years. The almost startling lack of poliomyelitis in natives of El Paso has long been a matter of interest to local physicians. In thinking back upon this over a period of many years it has seemed almost incredible that El Paso has escaped any appreciable incidence of poliomyelitis in its native citizens. In contemplating this problem, it occurred to the author to seek something in the medical situation in El Paso which was different from anywhere else in the United States. One thing stands out above all others and that is the very high incidence of the entity known as virus diarrhea and enteritis which occurs in infants, children and adults and which is quite endemic in this community. Practically everyone living in El Paso has this disease one to six times a year. In small children the disease is serious and if not treated promptly will quickly cause the infant's death. In small children the disease is more serious than in older children and adults. In the latter group it is not at all serious and rarely does the patient miss more than one or two days from his regular occupation. Generally the disease does not cause any time to be lost from the patient's occupation in this age group.

Chart I. The unusual incidence of poliomyelitis and enteritis in this city is responsible for the writing of this paper.

EL PASO, TEXAS — POPULATION IN 1940—96,810

	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
Death rate of diarrhea and enteritis (per 100,000 pop.)	66.3	81.8	86.5	78.2	54.2	64.5	65.7	44.7	34.2	48.0
Incidence of poliomyelitis (per 100,000 pop.)	0	0	6.1	2.8	0.9	3.6	10.1*	0	28.9*	6.8

*Many cases in these years were in transient military personnel.

In all probability the majority of the cases of enteritis found in El Paso are of a special type and are due to a virus. Some research work on this was done in El Paso in 1941 and no definite bacterial cause was found. It is true that bacillary dysentery, diarrhea and enteritis due to the enteritidis group, amebiasis, and diarrhea and enteritis due to contaminated foods are also present in El Paso. However, all these other types are in the great minority in that city. Virus enteritis is a quite easily communicable disease.

It is felt by the authors that it is likely that the virus enteritis is in some way related to the virus of poliomyelitis possibly somewhat as cowpox is to smallpox and this is the main thesis of this paper. Constant re-infection with virus enteritis keeps the population's immunity to poliomyelitis at a high level and when polio is contracted it is non-paralytic and usually unrecognized. This situation prevents an epidemic of poliomyelitis and keeps the incidence of paralytic poliomyelitis down to a low level.

Certain other aspect of the situation in El Paso would lend support to this idea. The incidence of poliomyelitis in the mountainous regions with a cool climate near El Paso is much greater per capita than it is in El Paso. The virus enteritis so common in El Paso is very much less common or absent in these areas.

During the Second World War there was stationed in El Paso a large number of soldiers and after the War for a considerable length of time there was a considerable military population here which was of a floating nature and with most of the soldiers not staying in El Paso any appreciable length of time. Many of these soldiers had their families with them. In the year 1946 El Paso had an appreciable number of poliomyelitis cases but the per capita incidence in soldiers and their dependents was approximately ten times that of the local population. The probable reason for this is that the soldiers and their families who contracted poliomyelitis had not lived in El Paso long enough to get a virus enteritis and thereby raise their immunity to poliomyelitis. This is felt to be of significance and lends support to the idea that the local citizens in El Paso are relatively more immune to poliomyelitis than people living elsewhere.

In studying the incidence of poliomyelitis in El Paso and the mortality from enteritis in children under two years it is quite apparent that during the years when the enteritis mortality is high the polio incidence is low and during the years that the enteritis mortality is low the polio incidence is high. This would seem to indicate that the more prevalent the virus enteritis is, the more immunity there is to poliomyelitis. The detailed figures for El Paso are presented in chart I. Some explanation of the statistics is in order. Figures were obtained for mumps because it was felt well to have data on additional virus disease as a control. Neither in El Paso or in the other cities studied was it possible to correlate mumps with either enteritis or polio. Only deaths in children under two years from diarrhea and enteritis are reportable and for this reason these figures were used. No accurate

report of the number of cases (incidence rate) for virus enteritis was obtainable and therefore this data could not be included in this study. The incidence of poliomyelitis is a much larger figure than the death rate for this disease. For this reason this figure is more helpful for comparative studies and therefore it was used.

Twenty-eight questionnaires in regard to poliomyelitis, enteritis and mumps in children for a ten-year period from 1938 to 1947 were sent to twenty-eight widely scattered cities of approximately the same size as El Paso. Eleven of these were returned with answers in form suitable for comparative study.

Of the eleven cities submitting usable answers to the questionnaire, ten of them show statistical findings which are very much alike but which are far different from El Paso. These ten cities which are scattered all over the United States, show a death rate of enteritis which is low and an incidence of poliomyelitis which is high in the group as a whole as compared with El Paso. Moreover when the incidence of poliomyelitis is low the death rate from enteritis is low. When the poliomyelitis incidence is high the enteritis death rate is high. It will be noted that the relationship between poliomyelitis and enteritis was not the same as it was in El Paso. In the other cities the incidence of poliomyelitis and enteritis varied together while in El Paso when one was up the other was down which was diametrically opposite to the situation in the other cities. In the reports received from the ten cities there was no correlation whatever between mumps and either poliomyelitis or the virus enteritis. The figures for one of these cities is shown in chart II, and presents an average for the ten cities which were quite like one another.

Chart II. A City with typical statistics.

Charlotte, North Carolina	Population in 1940—100,899									
	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
Death rate of diarrhea and enteritis (per 100,000 pop.)	6 2	6 05	4 95	20 4	7 65	13 2	20 3	14 5	0	5 3
Incidence of poliomyelitis (per 100,000 Pop.)	0	6 05	2 97	14 6	1 9	0	17 6	8 2	2 7	6 2

There was one city reporting which was different from both El Paso and the group of ten which were similar to one another. This city was Corpus Christi, Texas which showed the following phenomena. There was a high death rate from enteritis and a high incidence of poliomyelitis in Corpus Christi. When the death rate from enteritis was low the poliomyelitis incidence was low. When the death rate from enteritis was high the incidence of poliomyelitis was high. This situation paralleled El Paso and would militate somewhat against the theory expounded in this paper. However, when one recalls that this is one city which is quite different from a group of ten others it does not seem so important. One thing is evident in the Corpus Christi figures which is a gradual decline of the death rate from enteritis to a reasonably low level over a period of years, gradually

improving, whereas the incidence of poliomyelitis has been high during various years throughout the ten year period. The author has an explanation for these phenomena. It is felt that the enteritis in Corpus Christi is largely of the bacillary dysentery type whereas the enteritis in El Paso is largely of the virus type. The peculiar virus enteritis found in El Paso will account for the high over-all incidence of enteritis here while the absence of this virus enteritis in various other cities throughout the country will account for their low incidence of enteritis.

Comment

It would seem from the over-all picture of the statistics studied in El Paso and in the eleven cities where usable questionnaires were returned that there is at least some support statistically for the supposition outlined in the first part of this paper to the effect that in El Paso there is a virus enteritis which may be helpful in holding at an elevated level the titer of the immunity to poliomyelitis. This could probably be proved or disproved by virus research employing monkeys. The monkeys could be innoculated with the virus enteritis and then checked a short time afterward for the resistance to poliomyelitis. If their resistance to clinical poliomyelitis is greatly increased this would suggest a method of immunizing at least temporarily against poliomyelitis in the human. It is unfortunate that the immunity of the population in El Paso to the endemic virus enteritis is of short duration, probably not exceeding two months. This would mean that the person who is to be immunized for poliomyelitis would have to be very frequently immunized rather than being able to get a lasting immunity. However, this is not too discouraging a point considering the mild nature of the enteritis necessary to increase the immunity to poliomyelitis and considering furthermore the great desirability of avoiding clinical paralytic poliomyelitis. It might be that it would be necessary to immunize only during the period of increased seasonal incidence of poliomyelitis. It is hoped that this paper can be followed with another one subsequently by a virologist pursuing the line of thought outlined in this paper that the virus which causes endemic enteritis in El Paso is immunologically related to the virus of poliomyelitis.

Summary

A new idea is expressed that the virus producing endemic virus enteritis in El Paso, Texas is related to the virus of poliomyelitis as smallpox is related to cowpox.

Statistical information from El Paso and other cities tends to support this belief, although not conclusively.

Virus research with monkeys is proposed as a means of proving or disproving the idea.

If the relationship between the two viruses can be established, a means of developing at least temporary immunity to poliomyelitis is at hand.

News, Notes and Editorial Comments

MONOPLEX PLASTIC EYE UNIT NOW AVAILABLE

American Optical Company announces the availability of two small Monoplex plastic eye units containing 120 and 240 eyes respectively, both rights and lefts, in the most required and adaptable shapes.

Designed for use by ophthalmologists, hospitals and eye clinics desiring to carry a minimum stock of artificial plastic eyes, the two units are described in a new brochure in which all of the 120 eyes in 20 basic colors are shown in full color. Copies of the brochure are available upon request to AO Branch offices.

The smaller unit consists of 120 AO Monoplex plastic eyes in the 20 colors proved by experience to be those most frequently used. They are furnished in both rights and lefts in the three most required shapes: large oval, medium standard, and large standard.

The larger set with 240 eyes contains the same 20 popular colors in the shapes of the smaller unit plus two additional shapes: the small three-cornered and the large three-cornered, for convenience in more quickly adapting the eyes to unusual sockets. In addition, there is a duplication of colors in the most essential shape.

Both cases are bound in gold tooled, Morocco grain hide, have snap button closings and removable mahogany trays lined with champagne colored velvet. Special color assortments to meet individual requirements can be supplied.

The new brochure, as a prosthetic eye color chart, is the most accurate yet produced, according to the company, and is intended to be used for a guide in ordering Monoplex eyes. In addition to the full-color showing of eyes, each of the five basic eye shapes is shown.

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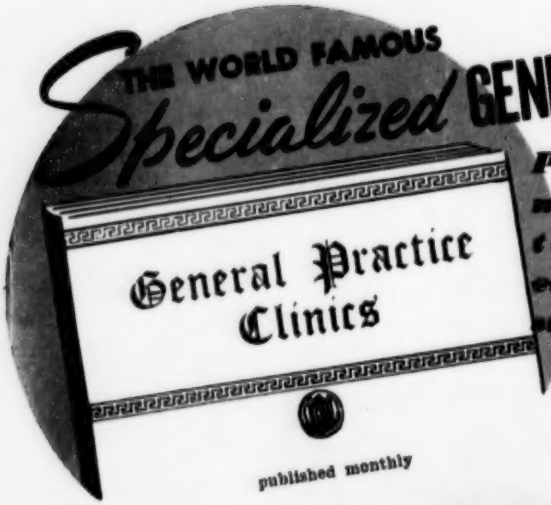

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